## REMARKS

Claims 7, 9, 11, 13, 15, 17 were pending. Claim 21 has been added. As such, Claims 7, 9, 11, 13, 15, 17, and 21 will be pending upon entry of this amendment. Support for the new claim can be found in the claims (*e.g.*, claim 7) as well as throughout the specification as originally filed. Thus, there is no new matter added as a consequence of the amendment.

**Claims 7, 11, 13, and 17 are not obvious**

Claims 7, 11, 13 and 17 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Di Bisceglie et al. ("Di Bisceglie") in view of either U.S. Patent No. 5,824,300 to Cummins or International Patent Publication No. WO 88/03411 to Cummins (collectively "Cummins"). The Examiner contends that it would have been obvious to one of skill in the art to use a liquid formulation containing 1-1500 IU of human leukocyte α-interferon as taught by Cummins for treating a patient infected with type C hepatitis ("HCV patient") as taught by Di Bisceglie.

Applicants respectfully disagree. To establish a *prima facie* case of obviousness, three basic criteria must be met. *M.P.E.P.* § 2142. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings. Second, there must be a reasonable expectation of success. Third, the combined prior art references must teach or suggest all of the claim limitations. The reasonable expectation of success and the teaching or suggestion to make the claimed combination must be found in the prior art *and* not be based on applicant's disclosure. *In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1981).

The present invention is directed to a peroral method of treating an HCV patient using a liquid formulation of human α-interferon isolated from stabilized lymphoblastoid or leukocytic cell lines. According to the present invention, human α-interferon is administered orally at a significantly lower doses than is taught by the prior art. The presently claimed daily doses (*i.e.*, 100 to 500 IU) are more cost effective, avoid undesirable side effects observed at higher doses, and are well tolerated by HCV patients. As evidenced in the Declaration of Renzo Brozzo Under Rule 132, which was submitted on May 2, 2001 to the U.S. Patent and Trademark Office in connection with the instant application, approximately one-half of the patients treated with oral human α-interferon demonstrated improvement over the long term (*i.e.*, a period of 24 weeks). *See* Declaration Under Rule 132, page 5, lines 6-7; page 5, lines 7, lines 2-6.

In contrast to the claimed invention, Di Bisceglie teaches treating HCV patients with daily subcutaneous injections of approximately one million units (*i.e.*, about 100,000 IU) of human α-interferon. Notably, the dose taught by Di Bisceglie is 100-200 times greater than the instantly claimed dose.

In addition, Di Bisceglie reported a long-term (*i.e.*, a period of 6-12 months) response rate of 10% (page 1510, col. 1, lines 15-28), which is far below the response rate observed when practicing the present invention. Indeed, Di Bisceglie observed that most patients relapsed after the treatment was discontinued (page 1510, col. 1, lines 2-4). Further, Di Bisceglie pointed to the administration of higher doses of α-interferon for longer periods of time as the likely reason why an earlier pilot study showed higher response rates. In view of the sub-optimal results obtained using one million units of human α-interferon, Di Bisceglie

recommended administering even higher doses of human α-interferon for longer periods of time ("Future studies should focus on higher doses of interferon alfa given for longer periods.").

Furthermore, one of skill in the art would expect that higher doses of human α-interferon would be required to obtain equivalent efficacy when administered orally as compared to intravenous administration. Thus, if greater than one million units of human α-interferon was contemplated for intravenous administration, the recommended dose of human α-interferon administered by the peroral route likely would be much higher.

Therefore, taken as a whole, Di Bisceglie points to use of much higher doses than the claimed dose range, which would have cautioned against treating HCV patients by the peroral route with 200 times less human α-interferon than advised by Di Bisceglie. As such, Di Bisceglie clearly teaches away from instantly claimed dose range of 100-500 IU, and cannot provide the motivation to combine its teachings with those of Cummins which does not relate to HCV treatment.

Cummins teaches administering 0.01 to 5 IU/lb human α-interferon to treat various immune disorders. According to the Examiner, this dose corresponds to 5 to 1,125 IU of human α-interferon per day. (*See* December 20, 2001 Office Action at page 4, lines 1-2). Cummins fails to teach or suggest administering human α-interferon to treat HCV patients. Furthermore, Cummins only teaches treating colds, cold sores, AIDS, and warts with low doses for short periods. Nowhere, however, does Cummins suggest combining its teachings relating to treatment of colds, cold sores, AIDS, and warts with Di Bisceglie's teachings relating to treatment of HCV. As such, neither Di Bisceglie nor Cummins provides any motivation to combine the respective teachings to arrive at the presently claimed invention.

Since Di Bisceglie is directed to the treatment of HCV and Cummins makes no mention of HCV, Di Bisceglie's teachings would carry more weight with respect to HCV treatment. Accordingly, even if the references were in hindsight considered together at the time of filing, the skilled artisan would have looked to Di Bisceglie for guidance on effective doses and mode of administration. Since Di Bisceglie teaches away from experimentation in the lower dose ranges, the skilled artisan would not have been motivated to try using the lower doses taught by Cummins, and thus could not have had a reasonable expectation of success. The claimed doses would simply have been considered ineffective, especially given the state of the art which demonstrated sub-optimal effectiveness using much higher doses, and the recommendations to push dose levels even higher.

The Examiner appears to maintain that the prior art, as a whole, invites the skilled artisan to attempt a range of doses of human α-interferon, including the range disclosed by Cummins. However, "obvious-to-try" is not the standard for obviousness in accordance with 35 U.S.C. § 103. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988). In the present case, Di Bisceglie clearly discourages experimentation at lower doses, thereby teaching away from the claimed invention. Moreover, the prior art collectively recommended treatment of HCV patients with high doses of human α-interferon for longer periods of time (instant specification at page 2, paragraph 0010). Without the motivation to experiment at the lower dose ranges, and with the recommendation in the art to use even higher doses of human α-interferon, the skilled artisan could not have had any reasonable expectation of success.

Not only does the prior art teach away from the claimed invention and negate any reasonable expectation of success, but practice of the claimed invention produced entirely unexpected results. The skilled artisan would not have expected that patients treated with human α-interferon at 100-200 times lower than the recommended doses (especially via the peroral route) would demonstrate a sustained, favorable response to such treatment. In fact, that is precisely what the inventors discovered. When compared to the long-term response rate of 10% reported by Di Bisceglie's high dose treatments, the patients treated in accordance with the claimed methods (*i.e.*, using a low dose of 100-500 IU) showed far greater improvement in the long term. Such unexpected results further support Applicants' position that the claimed methods are not at all obvious.

For the foregoing reasons, Applicants respectfully submit that claims 7, 11, 13 and 17 are patentable over the cited art, and request withdrawal of the rejection of these claims under 35 U.S.C. § 103(a).

**Claims 9 and 15 are not obvious**

Claims 9 and 15 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Di Bisceglie and Cummins, as applied to claims 7, 11, 13 and 7 above, and further in view of Ratajczak et al ("Ratajczak").

Ratajczak discloses the use of lozenges containing 50-100 IU human lymphoblastoid α-interferon for oropharyngeal delivery to treat patients infected with hepatitis B. For the same reasons discussed above regarding Cummins, Ratajczak would not provide any motivation for the skilled artisan to reach the claimed invention. For example, Ratajczak neither teaches nor suggests use of its α-interferon-containing lozenges to treat HCV. Also, Di

Bisceglie, Cummins, and Ratajczak do not teach or suggest a motivation to combine the cited references. Additionally, in light of the prior art, Ratajczak does not create a reasonable expectation of success. Accordingly, Applicants respectfully submit that claims 9 and 15 not obvious in view of Ratajczak, and request withdrawal of the rejection of these claims under 35 U.S.C. § 103(a).

## CONCLUSION

For all the foregoing reasons, Applicants respectfully request that all rejections be withdrawn and that the claims be allowed to issue.

A three (3) month extension to the period for responding to the instant Office Action is requested, and the appropriate fee set forth in 37 C.F.R. 1.17(a)(3) is enclosed. Applicants also enclose a Request for Continued Examination and the required fee. Applicants believe that no other fee is required in connection with this submission. However, should any other fee be required, the Commissioner is hereby authorized to charge any such fee to Deposit Account No. 02-4377. Two copies of this sheet are enclosed.

Respectfully submitted,

Date : August 26, 2003

Lisa B. Kole
PTO Reg. No. 35,225
(212) 408-2628

by:

Peter J. Shen
PTO Reg. No. 52,217
(212) 408-2595

BAKER BOTTS, L.L.P.
30 Rockefeller Plaza
New York, NY 10112
*Attorneys for Applicants*